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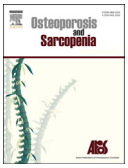
Osteoporosis and Sarcopenia 1 (2015) 127–133



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Original article

Higher free thyroxine levels are associated with sarcopenia in elderly Koreans

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Received 7 August 2015; accepted 22 October 2015
Available online 27 November 2015

Abstract

Background: Skeletal muscle is a major target of thyroid hormone action. Although sarcopenia is associated with adverse health outcomes in the elderly, few studies have examined the association between sarcopenia and thyroid hormone levels in elderly Asians. We investigated the relationship between thyroid hormone levels and sarcopenia in elderly Koreans.
Methods: 658 individuals (324 males and 334 females) ≥60 years old who visited the Health Screening and Promotion Center at Ajou University Hospital were recruited for the study. Whole-body dual-energy X-ray absorptiometry was performed, and gait speed and hand grip strength were measured. The rate and odds ratios for sarcopenia were calculated for free thyroxine (fT4) and thyroid stimulating hormone (TSH) levels.
Results: The fT4 concentration was negatively associated with muscle mass in males ($r^2 = 0.031$, $p = 0.001$) and females ($r^2 = 0.019$, $ps = 0.011$). The highest rate of sarcopenia occurred in the highest fT4 quartile in males and females. However, no significant differences were found among TSH quartiles in either sex. TSH was not significantly associated with the risk of sarcopenia in males or females, whereas the fT4 concentration was associated with the risk of sarcopenia in both sexes.
Conclusions: Higher fT4 levels, not lower TSH levels might have an adverse effect on sarcopenia especially in elderly people.

Keywords: Free thyroxine; TSH; Sarcopenia; Muscle

1. Introduction

Ageing is a global phenomenon. The advanced-age population within the Organisation for Economic Co-operation and Development (OECD) region outnumbered the youngest population (0–19 years old) in 2010 and is expected to surpass all other population age groups by 2020. South Korea is ageing faster than any other country in the OECD. In 2010, ~10% of the population was >65 years of age, and that proportion is estimated to be ~40% by 2050 [1].

Hypothyroidism and hyperthyroidism are common among the general population and are more prevalent in individuals aged >60 years [2,3]. Early diagnosis and treatment of overt thyroid dysfunction is crucial for this population in view of the marked effects of abnormal circulating thyroid hormone levels on a number of organ systems, including the heart, skeleton, and neurological systems [4]. Hypothyroidism is associated with impaired cognitive function [5] and medical conditions, such as hyperlipidemia, congestive heart failure, and macrocytic anemia, in the elderly population [6,7]. Furthermore,

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Peer review under responsibility of The Korean Society of Osteoporosis.

http://dx.doi.org/10.1016/j.afos.2015.11.001

overt hyperthyroidism is associated with significantly increased risks of cardiovascular disease, osteoporosis, and mortality, particularly among elderly individuals [4,7].

Sarcopenia is the age-associated loss of skeletal muscle mass resulting in decreased strength and aerobic capacity, leading to reduced functional capacity [8]. Previous studies have shown an association between sarcopenia and adverse health outcomes, such as falls, disability, hospital admission, long-term care placement, poor quality of life, and mortality, which highlights the importance of detecting and treating sarcopenia in older individuals [9].

Skeletal muscle is a major target of thyroid hormone action as demonstrated by the myopathic symptoms observed in patients with thyroid function disorders [10]. Hyperthyroidism can affect limb muscle mass and strength [11]. However, few studies have investigated the association of sarcopenia with thyroid hormone concentrations in the elderly Asian population. We investigated the relationship between thyroid hormone levels and the rate of sarcopenia in healthy Korean males and females ≥60 years old.

2. Materials and methods

2.1. Subjects

We recruited individuals aged ≥60 years who visited the Health Screening and Promotion Center at Ajou University Hospital (Suwon, Republic of Korea) for a routine medical examination between April 2011 and July 2014. Whole-body dual-energy X-ray absorptiometry (DXA) was performed, and gait speed and hand grip strength were measured in 666 of 747 participants. We excluded five individuals who were diagnosed with thyroid disease and currently taking thyroid hormone or anti-thyroid drugs and three individuals without thyroid hormone concentration measurements. Thus, 658 subjects (324 males, 334 females) were included in the study. Informed consent was obtained from all participants. Our study was approved by the Institutional Review Board of Ajou University Hospital (IRB number: AJIRB-MED-MDB-11-034).

2.2. Anthropometric parameters, grip strength, and gait speed measurements

Height and body weight were measured using standard methods, with subjects wearing light clothing. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). Waist circumference was measured midway between the lower rib margin and the iliac crest in a standing position. Blood pressure was measured after resting for 10 min in a sitting position using an automatic sphygmomanometer (TM-2655P; P.M.S (Instruments) Ltd., Berkshire, UK). Appendicular skeletal muscle masses (ASM) were acquired using DXA (Lunar iDXA, the GE Healthcare Lunar, Madison, WI, USA). ASM was calculated as the sum of muscle mass in arms and legs, assuming that all non-fat and non-bone tissue is skeletal muscle. Daily quality control scans were performed during the study period. Subjects were scanned using standard imaging and positioning protocols. Muscle strength was assessed by grip strength, which was measured using a Jamar® Plus Digital Hand Dynamometer (Sammons, Preston, IL, USA). Testing was performed with the participant in the sitting position with the elbow flexed at 90°. Measurements were taken for each hand, and the participant was encouraged to exert the greatest force possible. The strongest hand-grip strength was used in the analyses. Physical performance was assessed by usual walking speed. Participants were asked to walk straight for 8 feet (2.4 m) at their usual speed.

2.3. Laboratory measurements

Fasting blood samples were drawn at the antecubital area between 08.00 and 11.00 h. Serum samples were stored at 4 °C and analyzed within 1 day after sampling. Blood urea nitrogen, fasting glucose, liver enzymes, and lipid profiles were measured using an automatic analyzer (Toshiba TBA 200FR; Toshiba Medical System Co. Ltd, Tochigi-ken, Japan). Low-density lipoprotein cholesterol levels were calculated from the levels of total cholesterol, triglycerides (TG) and high-density lipoprotein cholesterol. The concentration of 25-hydroxyl vitamin D was assayed using a radioimmunoassay kit (DiaSorin, Stillwater, MN, USA). Thyroid stimulating hormone (TSH) and free thyroxine (fT4) levels were measured using enzyme immunoassays (Advia Centaur Immunodiagnostic system, Siemens Healthcare Diagnostics, Tarrytown, NY, USA). The reference ranges were 0.55−4.78 uIU/mL for TSH and 0.89−1.76 ng/dL for fT4.

2.4. Covariates

The participants completed standardized questionnaires on smoking and drinking status, medication history, and medical histories of hypertension, type 2 diabetes, and cardiovascular and cerebrovascular diseases. Smoking history was categorized as current smoker or non-smoker. Drinking was categorized as current drinker or non-drinker.

2.5. Definition of sarcopenia

The height adjusted ASM (ASM/height^2) was used to define the sarcopenia cases according to the recommendation of the Asian Working Group for Sarcopenia (AWGS) [9]. Low muscle mass was defined as 1 standard deviation below the mean muscle mass of the young reference group [12] instead of 2 standard deviation as recommended by AWGS because too small number of subjects were classified as sarcopenia cases with this criteria. From these data, ASM/height^2 (m^2) was determined to be < 7.50 kg/m^2 in males and <5.38 kg/m^2 in females. The lowest grip strength or gait speed quartile was classified as low muscle strength or gait speed, respectively, because no reference cut-off values are available for the diagnosis of sarcopenia in Korean individuals.

The diagnosis of sarcopenia was based on the European Working Group on Sarcopenia in Older People (EWGSOP)

recommendations for muscle mass, muscle strength, and physical performance [13]. Sarcopenia was characterized by reduced muscle mass and strength and poor physical performance.

2.6. Statistical analysis

Subjects were grouped according to sex, and male and female data were analyzed separately. TG, fT4, TSH, and grip strength were not normally distributed; thus, logarithmic conversions were performed to approximate a normal distribution.

Baseline characteristics were compared between the non-sarcopenia and sarcopenia groups using Student's *t*-tests for continuous variables and chi-squared tests for categorical or ordinal variables. Pearson's correlation analyses were performed according to sex to determine whether fT4 or TSH was associated with parameters related to sarcopenia (muscle mass, grip strength, and gait speed). The fT4 and TSH data were divided into quartiles, and the rate of sarcopenia for each quartile was calculated according to sex. A logistic regression analysis was used to calculate the odds ratios (ORs) for fT4 and TSH. Two models were constructed: Model 1, adjusted for age, BMI, vitamin D, fasting glucose, log alanine aminotransferase (ALT), and log aspartate aminotransferase (AST), and Model 2, further adjusted for comorbidities (diabetes, hypertension, cardiovascular disease, and cerebrovascular disease) and current smoking and drinking statuses. All statistical tests were conducted using the Statistical Package for the Social Sciences version 19.0 (SPSS Inc., Chicago, IL, USA). Two-sided p <0.05 were deemed to indicate statistical significance.

3. Results

The baseline characteristics of the subjects are shown in Table 1. Age was significantly higher in both males and females in the sarcopenia group than the non-sarcopenia group. Height, weight, BMI, and waist circumference of males and females were significantly lower in the sarcopenia group than the non-sarcopenia group. Fasting glucose was significantly higher and vitamin D levels, AST, and ALT significantly lower in males in the sarcopenia group compared with the non-sarcopenia group. The proportion of current smokers in the sarcopenia group was significantly higher among females, but not males, compared with the non-sarcopenia group. fT4 levels were significantly higher among females, but not males, in the sarcopenia compared with the non-sarcopenia group. In contrast, TSH levels were not significantly different between groups in either males or females. The correlations of fT4 and TSH levels with the components of sarcopenia are shown in Figs. 1 and 2. fT4 was negatively associated with muscle mass

Table 1
Baseline characteristics of the study population.

	Males			Females		
	Non-sarcopenia (n = 241)	Sarcopenia (n = 83)	*p*	Non-sarcopenia (n = 301)	Sarcopenia (n = 33)	*p*
Age (y)	65.4 ± 4.2	68.3 ± 5.9	<0.001	65.5 ± 4.3	68.3 ± 4.4	<0.001
Height (cm)	167.1 ± 5.6	165.3 ± 5.3	0.010	153.9 ± 5.5	150.3 ± 5.3	<0.001
Weight (kg)	69.8 ± 8.7	61.9 ± 7.3	<0.001	58.1 ± 8.2	48.2 ± 6.1	<0.001
Body mass index (kg/m^2)	25.0 ± 2.7	22.7 ± 2.4	<0.001	24.5 ± 3.1	21.3 ± 2.3	<0.001
Waist circumference (cm)	88.5 ± 7.7	82.6 ± 11.5	<0.001	87.9 ± 8.8	81.6 ± 7.4	<0.001
Systolic blood pressure (mmHg)	124.0 ± 15.1	128.1 ± 14.8	0.033	125.2 ± 16.9	128.4 ± 18.2	0.297
Diastolic blood pressure (mmHg)	79.7 ± 10.0	80.2 ± 10.5	0.718	75.1 ± 10.8	76.8 ± 10.5	0.369
Total cholesterol (mg/dL)	188.6 ± 38.3	185.8 ± 37.6	0.557	206.4 ± 37.9	203.5 ± 36.1	0.678
Triglyceride[a] (mg/dL)	124.8 ± 75.3	116.6 ± 71.4	0.355	107.6 ± 54.8	115.6 ± 74.1	0.483
HDL-cholesterol[a] (mg/dL)	47.8 ± 10.8	49.6 ± 16.5	0.412	54.7 ± 13.0	58.5 ± 13.9	0.118
Fasting glucose (mg/dL)	102.0 ± 18.6	110.7 ± 32.1	0.039	101.6 ± 23.7	103.7 ± 31.9	0.899
AST[a] (IU/L)	32.2 ± 16.5	27.9 ± 10.1	0.006	30.0 ± 11.9	27.2 ± 10.1	0.054
ALT[a] (IU/L	30.1 ± 17.8	25.6 ± 13.4	0.017	24.2 ± 15.4	20.1 ± 9.4	0.066
Vitamin D (ng/mL)	16.5 ± 7.3	14.4 ± 6.3	0.023	15.3 ± 8.1	14.8 ± 8.1	0.736
BUN (mg/dL)	13.3 ± 3.6	13.3 ± 3.4	0.995	12.2 ± 3.5	12.6 ± 3.7	0.553
Free T4[a] (ng/dL)	1.21 ± 0.25	1.26 ± 0.25	0.095	1.18 ± 0.21	1.26 ± 0.22	0.047
TSH[a] (uIU/mL)	2.04 ± 1.90	2.08 ± 1.35	0.536	2.67 ± 2.79	2.40 ± 1.65	0.925
Muscle mass[b] (kg/m^2)	7.60 ± 0.76	6.53 ± 0.78	<0.001	6.02 ± 0.64	4.98 ± 0.37	<0.001
Grip strength[a] (kg)	38.6 ± 6.6	31.7 ± 5.4	<0.001	22.6 ± 4.8	18.3 ± 3.5	<0.001
Gait speed (m/s)	1.59 ± 0.24	1.34 ± 0.22	<0.001	1.40 ± 0.25	1.14 ± 0.22	<0.001
Type 2 diabetes	15.4%	28.9%	0.030	12.0%	15.2%	0.744
Hypertension	49.2%	48.2%	0.729	39.3%	30.3%	0.510
Cardiovascular disease	6.7%	8.4%	0.622	7.0%	0.0%	0.242
Cerebrovascular disease	2.1%	4.8%	0.305	2.3%	0.0%	0.568
Current smoker	19.7%	30.9%	0.097	1.5%	10.3%	0.011
Current drinker	62.6%	56.1%	0.360	14.6%	23.3%	0.095

HDL: high density lipoprotein, AST: aspartate aminotransferase, ALT: alanine aminotransferase, BUN: blood urea nitrogen, TSH: thyroid stimulating hormone.
[a] Log transformed.
[b] Muscle mass = Appendicular skeletal muscle mass/height^2.

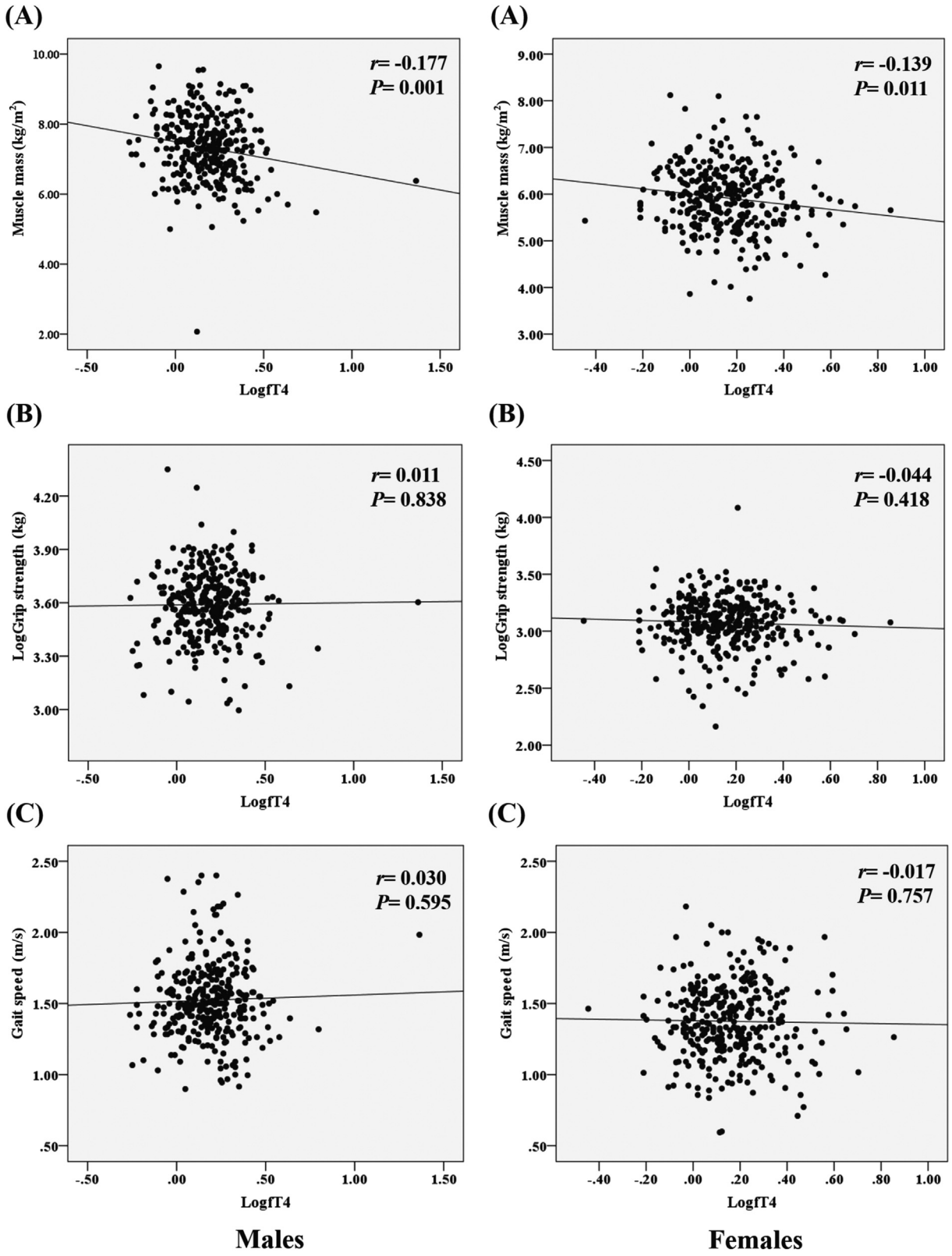

Fig. 1. Correlations between fT4 levels and sarcopenia components (muscle mass (A), grip strength (B), and gait speed (C)) according to sex.

in both males ($r = -0.177$, $p = 0.001$) and females ($r = -0.139$, $p = 0.011$). In contrast, TSH was not significantly associated with muscle mass in either sex. No significant associations were found between thyroid function (fT4 and TSH levels) and grip strength or gait speed. Fig. 3 shows differences in sarcopenia rates across fT4 and TSH

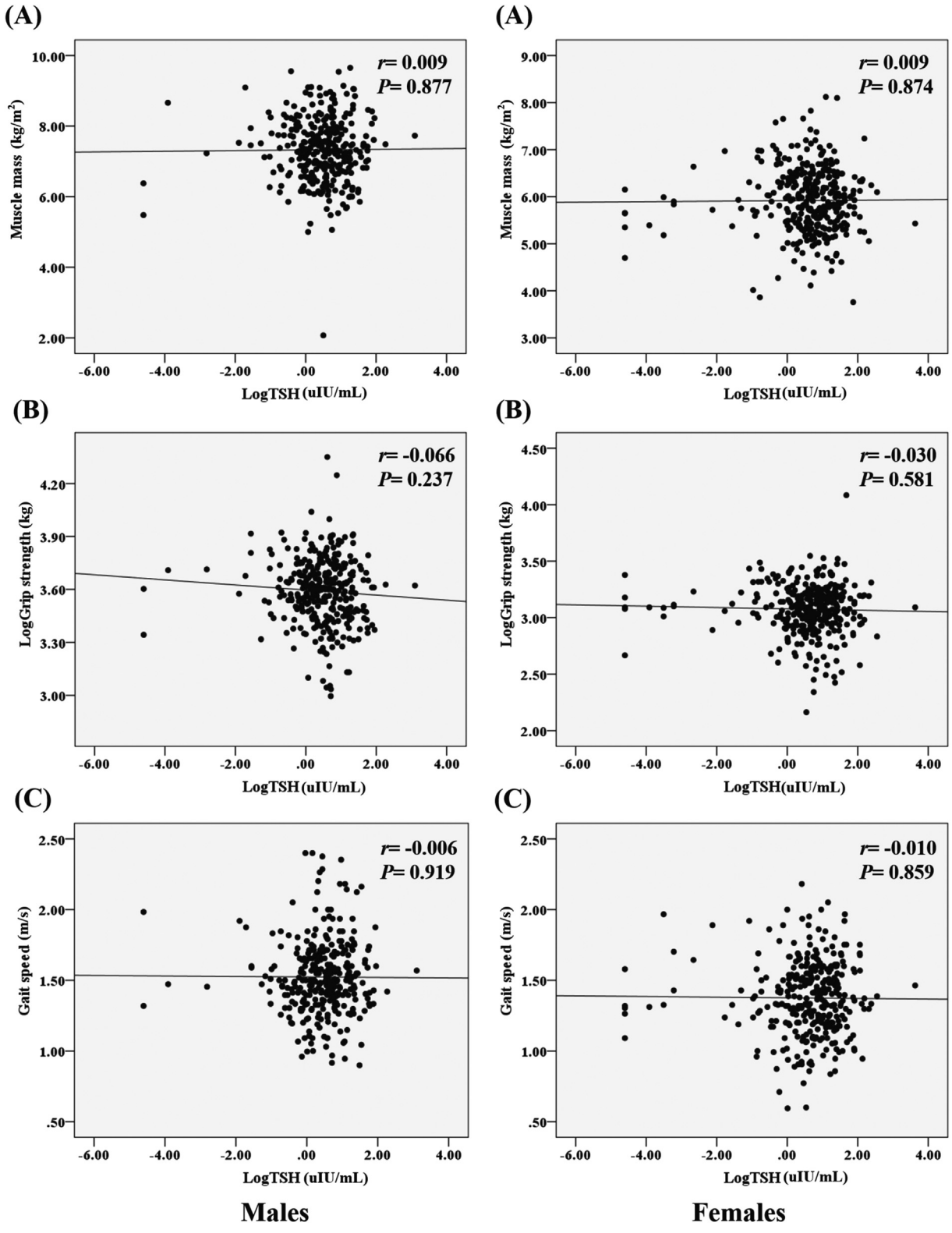

Fig. 2. Correlations between TSH levels and sarcopenia components [muscle mass (A), grip strength (B), and gait speed (C)] according to sex. TSH: thyroid stimulating hormone.

quartiles according to sex. The highest rate of sarcopenia was seen in the highest fT4 quartile in males and females, whereas the lowest rate occurred in the second to lowest quartile in both sexes. In contrast, the rate of sarcopenia was not significantly different across TSH quartiles in either sex. Table 2 shows the risk of sarcopenia for males and females within the upper fT4 and TSH quartiles. fT4 concentration was significantly associated with the risk of sarcopenia in males (Model 1: OR = 1.45, 95% confidence interval (CI) = 1.11−1.89, p = 0.005; Model 2: OR = 1.56, 95%

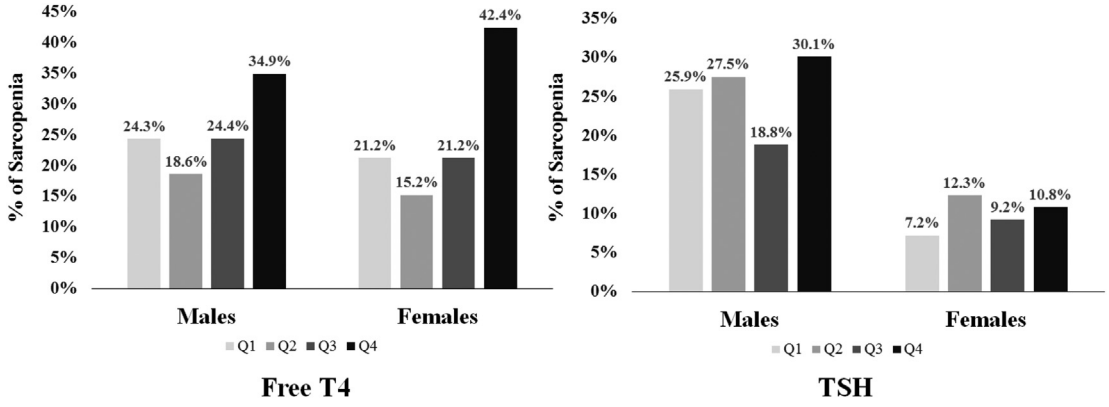

Fig. 3. Differences in sarcopenia rates across fT4 and TSH quartiles. TSH: thyroid stimulating hormone.

CI = 1.17−2.07, p = 0.003) and females (Model 1: OR = 1.53, 95% CI = 1.04−2.26, p = 0.031; Model 2: OR = 1.72, 95% CI = 1.10−2.68, p = 0.018). TSH was not significantly associated with the risk of sarcopenia in either sex.

4. Discussion

We found that higher fT4 levels were associated with sarcopenia in relatively healthy elderly Koreans.

Furthermore, the fT4 concentration was highly associated with muscle mass. Muscle function is impaired in patients with thyrotoxicosis or hypothyroidism [10], and a previous study found that excess thyroid hormone impaired the regeneration process in the mdx mouse [14]. Recently, thyroid hormone-related impairment was shown to be the result of massive satellite cell apoptosis, via the FoxO3/MyoD axis, caused by the direct exposure of activated satellite cells to circulating thyroid hormone [15]. Furthermore, a recent study showed that reduced muscle mass and function may be associated with elevated resting metabolic rate with declining health in elderly individuals [16]. Thyroid hormones affect energy expenditure, particularly resting metabolic rate [17]. Although we did not measure the metabolic rate of the subjects, the reduced muscle mass observed in our study may be indirectly attributed to an increase in resting metabolic rate resulting from high fT4 levels.

Table 2
Odds ratios (ORs) for sarcopenia in the upper fT4 and TSH quartiles.

Model	fT4 ng/dL			TSH uIU/L		
	OR	95% CI	p	OR	95% CI	p
Males						
Model 1	1.45	1.11−1.89	0.005	0.96	0.75−1.23	0.761
Model 2	1.56	1.17−2.07	0.003	0.95	0.73−1.24	0.722
Females						
Model 1	1.53	1.04−2.26	0.031	1.00	0.69−1.44	0.981
Model 2	1.72	1.10−2.68	0.018	0.87	0.58−1.31	0.510

Model 1: Adjustment for age, BMI, vitamin D, fasting glucose, log ALT, and log AST.
Model 2: Adjustment for age, BMI, vitamin D, fasting glucose, log ALT, log AST, comorbidities (diabetes, hypertension, cardiovascular disease, and cerebrovascular disease) and current smoking and drinking statuses.
ALT: alanine aminotransferase, st: aspartate aminotransferase, BMI: body mass index, TSH: thyroid stimulating hormone

We found no association between sarcopenia rate and TSH levels. The thyroid hormone physiology of elderly individuals differs from that of younger individuals. Thus the TSH distribution curve in older adults shifts to higher values compared with younger adults [18]. Two longitudinal studies showed an increase in serum TSH levels with ageing, but no change in fT4 concentrations [19,20]. Thus, changes in serum TSH levels may not reflect thyroid disease in elderly individuals. In fact, fT4, but not TSH, has been associated with all-cause mortality [21,22]. TSH concentrations reflect the pituitary effects of thyroid hormones, which may differ from end-organ effects. A previous study found that TSH was strongly associated with outcomes affecting the brain (i.e., dementia), whereas the fT4 associations were strongest for outcomes directly involving the heart (atrial fibrillation and heart failure) [23]. A previous study in elderly Koreans found that increased TSH levels were not associated with sarcopenia, and that subclinical hypothyroidism may not be related to sarcopenia [24]. These findings may be explained by the fact that TSH rather than fT4 levels were measured.

We found no association between thyroid hormone levels and grip strength or gait speed. However, a previous study using the InCHIANTI study cohort revealed that mild excess of thyroid hormone was associated with decreased physical function in elderly males [25]. We enrolled subjects who had visited a center, suggesting that they were in relatively good health, perhaps making it difficult to reveal a clear association between thyroid hormone levels and physical function. The association between thyroid hormone levels and physical function needs to be re-evaluated in the general population.

Several studies have found an association between mortality and fT4 levels [21,22]. Sarcopenia is a risk factor for mortality [26]. Although, multiple morbidities, such as atrial fibrillation and heart failure, may be related to high thyroid hormone levels, sarcopenia resulting from high fT4 concentrations may contribute to mortality rate in elderly individuals.

Our study has several strengths. Although several experimental studies have investigated the effect of thyroid hormone levels on muscle function, few have examined the relationship between muscle function and thyroid hormone levels in

humans. Furthermore, to our knowledge, no study has reported an association between sarcopenia diagnosed according to the EWGSOP criteria and thyroid hormone concentrations in an elderly Asian population.

Our study has some limitations. First, we used a cross-sectional design; thus, although we were able to demonstrate associations between sarcopenia and thyroid hormone levels, we were not able to establish causal relationships. Second, we recruited participants who had visited a screening center; thus, our study population was not representative of the general population. However, our finding of a significant association between fT4 levels and sarcopenia in a small sample of relatively healthy elderly individuals is meaningful. Third, we did not obtain second measurements of circulating TSH and fT4 concentrations; thus, we cannot rule out the possibility that the changes in TSH levels may have been transient in some patients. Fourth, nutrition and physical activity are two major determinants of muscle mass. Regretfully, we did not measure these parameters. Fifth, sex hormones, especially testosterone are important determinants of muscle mass. Sex hormones were not measured in this study. However, we did not think that it could not significantly affect the result of this study because thyroid hormone is not directly affected by sex hormones.

In conclusion, higher fT4 levels, not lower TSH levels might have an adverse effect on sarcopenia especially in elderly people. Future prospective studies are needed to investigate the associations of excess thyroid hormone or replacement therapy with adverse effects on muscle mass and physical function in the general population.

Conflicts of interest

The authors declare no conflicts of interest.

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